

SUPPORT FOR THE AMENDMENTS

Claims 1, 2, 4-8, 11-17, and 23-38 were previously canceled.

Claims 3 and 18-21 have been amended.

The amendment to Claims 3 and 18-21 is supported by the corresponding claims as originally filed and the specification throughout.

No new matter has been added by the present amendments.

REMARKS

Claims 3, 9, 10, and 18-22 are pending in the present application.

At the outset, Applicants wish to thank Examiner Tsay for the helpful and courteous discussion with their undersigned representative on July 23, 2009. During this discussion, the lack of applicability of Himmelspace et al to Claim 3 under 35 U.S.C. §102(e) was discussed. The Examiner indicated that the finality of the May 8, 2009 Office Action would be withdrawn and prosecution reopened. The Office Action mailed August 10, 2009, is the response of this discussion. Reconsideration of the outstanding rejections is requested.

The objection to Claims 3 and 18-21 is obviated by amendment. Each of these claims have been amended to insert the article “a” at the beginning of each claim. Thus, this ground of objection is believed to be moot. Withdrawal of this ground of objection is requested.

The rejection of Claims 3, 9-10, and 18-22 under 35 U.S.C. §112, first paragraph (written description), is respectfully traversed.

The Examiner alleges that Claims 3, 9-10, and 18-22 fail to comply with the written description requirement because these claims are drawn to a factor X analogue having only the structural limitation of a modification in its activation site and rejects the claims for a lack of structure other than the active site sequence.

Applicants submit that the presently claimed invention is drawn to a factor X presenting a very specific mutation in its activation site. The scope and nature of the term “factor X” is well known in the art and, as such, the meaning of “factor X analogue” as described and

claimed in the present application would be readily apparent to the skilled artisan in view of the disclosure of the present specification.

First, as set forth at page 6, lines 21-23 of the present specification, the “factor X analogue” refers to both mature factor X molecule and its molecular precursor.

In addition, please argue that the factor X analogue according the invention presents a very specific mutation of the activation site, which is proceeded on:

- a native factor X, but also on
- a factor X with modifications concerning others domains than its activation site as specified at page 6, line 34 to page 7, line 2, page 9, lines 17-23 of the present specification.

It is highly important to understand that, in both cases, the very specific mutation defining the factor X analogue according the invention, is proceeded on a factor X presenting **a native activation site.**

Thus, Applicants submit that the wording of the claims clearly define the subject matter of those claims, since the structural limitation reside, not only in SEQ ID NO: 9, but also in the structure of Factor X (native or presenting modifications as disclosed at page 6, line 34 to page 7, line 2, page 9, lines 17-23 of the present specification). As such, Applicants submit that the scope and meaning of the claimed invention is clear to the skilled artisan and the written description requirement of 35 U.S.C. §112, first paragraph, has been complied with.

Withdrawal of this ground of rejection is requested.

The rejection of Claim 22 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

The Examiner objects that the expression “medicinal product” in claim 22 is unclear. Applicants disagree.

Applicants wish to remind the Examiner that: “Applicants are their own lexicographer” (MPEP §2173.01). MPEP §2173.01 also states that Applicants “can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art.” Further, definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP §2173.02).

To this end, Applicants refer the Examiner to the fact that “medicinal product” is defined by the European Directive 2001/83/EC (copy **submitted herewith**) at Title 1, Article 1, Section 2 as follows:

“Medicinal product:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
- (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”*

In view of the foregoing, Applicants submit that the scope and meaning of the expression “medicinal product” and “procoagulant medicine product” is clearly defined and does not require any further clarification.

Withdrawal of this ground of rejection is requested.

The rejections of: (a) Claims 3, 18, and 22 under 35 U.S.C. §103(a) over Himmelspace et al, (b) Claims 19-21 under 35 U.S.C. §103(a) over Himmelspace et al, and (c) Claims 9-10 under 35 U.S.C. §103(a) over Himmelspace et al, are respectfully traversed.

Independent Claim 3 is drawn to a factor X analogue having the sequence Leu-Thr-Arg-Ile-Val-Gly (SEQ ID NO: 1) of the activation site of native factor X replaced with the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9). Applicants respectfully submit that Himmelspace et al fails to disclose or suggest this specific mutation with sufficient particularity to support an anticipation and/or obviousness rejection.

Himmelspace et al disclose Factor X analogues having the generic sequence:

Gly228-R6-R5-R4-R3-R2-Arg234-R I,

wherein:

- a) R1 is an amino acid selected from the group consisting of Ile, Val, Ser, Thr, and Ala,
- b) R2 is an amino acid selected from the group consisting of Pro, Gly, Lys, and Arg,
- c) R3 is an amino acid selected from the group consisting of Phe, Lys, Met, Gln, Glu, Ser, Val, Arg, and Pro
- d) R4 is an amino acid selected from the group consisting of Asp, Ile, Ser, Met, Pro, Thr, Arg, Lys,
- e) R5 is an amino acid selected from the group consisting of Asn, Lys, Ser, Glu, Ala, Gln, His, and Arg, and
- f) R6 is an amino acid selected from the group consisting of Asp, Phe, Thr, Arg, Leu, and Ser.

Himmelspace et al fail to disclose or suggest a factor X analogue having the sequence Leu-Thr-Arg-Ile-Val-Gly (SEQ ID NO: 1) of the activation site of native factor X replaced with the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) with sufficient specificity and the artisan would have no reason to select this factor X analogue from the extensive list of

alternative factor X analogues, much less an expectation of the beneficial results flowing from the same.

Indeed, as stated above Himmelspace et al merely disclose an extensive list of alternative factor X analogues and provides a generic disclosure, which can definitely not be considered as anticipating the very specific and particular combination of substituent which characterizes the analogue of factor X according to the present application.

Applicants direct the Examiner's attention to the fact that the object of the present application is a factor X, initially with a native activation site, in which said activation site is mutated between the position 232 and 237.

The native sequence of the activation site of factor X comprises the sequence:

Gly₂₂₈-Asn₂₂₉-Asn₂₃₀-Asn₂₃₁-Leu₂₃₂-Thr₂₃₃-Arg₂₃₄-Ile₂₃₅-Val₂₃₆-Gly₂₃₇

The factor X according the invention is mutated so that the sequence Leu₂₃₂-Thr₂₃₃-Arg₂₃₄-Ile₂₃₅-Val₂₃₆-Gly₂₃₇ of the native activation site of factor X is replaced with the sequence Val₂₃₂-Pro₂₃₃-Arg₂₃₄-Ala₂₃₅-Val₂₃₆-Gly₂₃₇.

The factor X analogue according to the present invention thus comprises, in its activation site, the sequence:

Gly₂₂₈-Asn₂₂₉-Asn₂₃₀-Asn₂₃₁-**Val₂₃₂-Pro₂₃₃-Arg₂₃₄-Ala₂₃₅-Val₂₃₆-Gly₂₃₇**

The Examiner alleges that Himmelspace et al disclose a factor X analogue comprising the sequence:

Gly₂₂₈-**R₆**₂₂₉-R₅₂₃₀-R₄₂₃₁-Val₂₃₂-Pro₂₃₃-Arg₂₃₄-Ala₂₃₅-Val₂₃₆-Gly₂₃₇

Himmelspace et al claim in column 83 that:

- R₄ is an amino acid selected from the group consisting of Asp, Ile, Ser, Met, Pro, Thr, Arg, Lys. Nevertheless, Himmelspace et al also disclose at column 6 that "R₄= Asn, Asp, Ile, Ser, Met, pro, Thr, Lys or Arg".

- R5 is an amino acid selected from the group consisting of Asn, Lys, Ser, Glu, Ala, Gln, His, and Arg.
- R6 is an amino acid selected from the group consisting of Asp, Phe, Thr, Arg, Leu, Ser.

Therefore, Himmelspach et al does not disclose the presence of Asparagine (Asn) at position 229 (amino acid R6).

Accordingly, the factor X analogue according to the invention certainly does not fall within the breath of the scope of compounds embraced by Himmelspach et al.

In addition, there is no incitation in Himmelspach et al that might lead the skilled artisan to the replacement of the native activation site of factor X with the specific sequence:

Val-Pro-Arg-Ala-Val-Gly.

The present application provides a very specific factor X analogue containing a thrombin cleavable sequence, without being prejudicial to the enzymatic activity of the activated factor X.

It is indeed reminded that the efficiency of cleavage is conditioned by the nature of the amino acids framing the cleavage site of factor X, and more specifically by the residues **P₃-P₂-P₁-P'₁-P'₂-P'₃** of the activation site, the cleavage occurring between the residues P₁ and P'₁.

The residues P'₁ to P'₃ are involved in the catalytic activity of factor X after activation.

Applicants remind the Examiner that, as in all serine protease, the N-terminal residues of the catalytic chain of activated factor X (including residues P'₁ to P'₃) are involved in the enzymatic activity.

The skilled artisan is acutely aware that it is not possible to predict the enzymatic activity of an activated factor X. It was thence not obvious for the skilled artisan to select the

exact configuration of residues which might comply with this absolutely essential feature of the invention.

As shown in the example of the present application, the inventors surprisingly discovered that substitution in the factor X sequence, at positions P_2 - P_1 - P'_1 of the sequence TR-I with the sequence PR-A makes it possible to obtain factor X analogues which can be effectively cleaved by thrombin.

In addition, the inventors discovered that this cleavage generates an activated factor X with a catalytic activity compatible with a normal physiological functions and having a longer half life than native activated factor X.

Moreover, the Examiner is reminded that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, Applicants further submit that the Examples of the present application, as presented herein below, are sufficient to overcome a *prima facie* case of obviousness.

a. The analogue according the invention is cleaved by thrombin and generates amidolytic activity

In their experiments, the inventors produced several analogues of factor X, as below (see Table I on page 10 of the specification):

	Factor X analogue	Sequence P₃-P₂-P₁-P'₁-P'₂-P'₃
SEQ ID No 7	GDX-IVG	VPR-IVG
SEQ ID No 8	GDX-IFG	VPR-IFG
SEQ ID No 9	GDX-AVG	VPR-AVG
SEQ ID No 10	GDX-IFR	VPR-IFR
SEQ ID No 11	GDX-SVG	VPR-SVG
SEQ ID No 12	GDX-SFR	VPR-SFR

In Example 4 of the present application, the inventors evaluated the rate of cleavage of the factor X analogues by thrombin, depending on whether or not this cleavage generates a detectable amidolytic activity. Those experiments made also possible the measurement of the amidolytic activity generated by the activated factor X analogues.

The experiment is a Michaelis Menten kinetics experiment, wherein:

- **K_m** is a constant that is equal to the substrate concentration at which an enzyme reaction proceeds at half the maximum velocity and is associated with the affinity of the enzyme (thrombin) for substrate (the zymogen derived from factor X) ;
- **k_{cat}** gives a direct measure of the catalytic production of product under optimum conditions ; and
- **k_{cat}/K_m** represent a measure of enzyme efficiency.

The inventors thus measured the rate constant which is directly proportional to the specificity constant (k_{cat}/K_m) of the enzyme (thrombin) for its substrate (the zymogen derived from factor X).

Table V of the present application (see page 21) puts in light the following facts:

- GDX-SVG, GDX-IVG, GDX-IFG and GDX-IFR are cleaved by thrombin but the reaction is too slow for it to be possible to estimate the value of the k_{cat}/K_m ;
- GDX-SFR analogue is cleaved very rapidly but does not generate detectable amidolytic activity ($k_{cat}/K_m=4.10^3 \text{ M}^{-1}.\text{s}^{-1}$) ; and
- GDX-AVG analogue is cleaved by thrombin and has readily detectable amidolytic activity ($k_{cat}/K_m=1.10^2 \text{ M}^{-1}.\text{s}^{-1}$).

This experiment corroborates the fact that VPR-SFR is highly favorable for cleavage by thrombin as described in the previous art.

Moreover, this experiment clearly evidences that VPR-AVG analogue is cleaved by thrombin, in a less extend than VPR-SFR, but surprisingly provide a higher amidolytic activity than the others factor X analogues.

b. The activated form of GDX-AVG analogue interacts with factor Va

Applicants evaluated in Example 5 of the present application the activation of prothrombin (which is naturally activated by factor Va and activated factor X).

This experiment clearly illustrates the fact that the addition of factor Va restore the catalytic activity of the activated form of GDX-AVG analogue. In addition, this experiment shows that factor Va does not provide such results with any of the others factor X analogues.

This indisputably indicates that the activated form of GDX-AVG analogue interacts with factor Va, and thus activate prothrombin.

c. The activated form of GDX-AVG analogue has a higher half life than its native homologue

In Example 5, Applicants determined the ability of each activated form of the factor X analogues to form a stable covalent complex with antithrombin. The inventors therefore determine the k_{on} of the interaction of antithrombin with the activated forms of the factor X analogue.

Physiologically, antithrombin is an inhibitor of the activated form of factor X and the value of its k_{on} for the interaction with activated form of factor X is about $10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$.

In this experiment, a lower value of the k_{on} of a factor X analogue suggests that its interaction with antithrombin is less effective, and thus that said analogue remains active for longer.

The results of this experiment are summarized in Table IX of the present application (see page 36):

- in absence of heparin, the values of k_{on} of the antithrombin for the activated form of GDX-AVG analogue is about $10 \text{ M}^{-1} \cdot \text{s}^{-1}$, i.e. more than 1000 times less than that of its non mutated homologue ($k_{on}=1.2 \cdot 10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$), and more than 10 to 100 times less than the k_{on} values of the others factor X analogues; and
- in presence of heparin, the value of the k_{on} of the antithrombin for the activated form of GDX-AVG ($k_{on}=3.01 \cdot 10^2 \text{ M}^{-1} \cdot \text{s}^{-1}$) is far lower than for the others factor X analogues.

This observation undoubtedly indicates that, after activation, the GDX-AVG analogue remains active for longer than its non-mutated homologue, which prolong the procoagulant action of the analogue and therefore considerably reinforce its anti-haemophilic properties.

To confirm this hypothesis, Applicants determined the plasma half life of the activated form of the factor X analogues by measuring their residual activity after incubation for a varying amount of time in a pool of normal human plasmas.

The results are summarized in Table X of the present application (see page 38):

- in presence of heparin, the half life of activated GDX-AVG analogue is about 5 minutes and 30 seconds, whereas the half lives of the others analogues are less than 30 seconds;
- in the absence of heparin, the half life of the activated form of GDX-AVG analogue is notably extended and is about 55 times longer than the others activated factor X analogues.

Those outstanding observations would clearly not have been obvious for the skilled artisan, on the basis of his general knowledge or in view of the teachings of Himmelspach et al.

d. The activated form of GDX-AVG analogue has a procoagulant activity

Applicants tested the procoagulant activity of the activated forms of the factor X analogues. The procoagulant activity of the factor X analogues is compared with that of the normal homologue lacking Gla domain (GD-FX).

Table XI of the present application (see page 40) shows that the activated form of GDX-AVG analogue shortens the clotting time as much as the activated form of the GD-FX analogue, which is not true for the other activated factor X analogues.

This result corroborates the fact that the GDX-AVG analogue clearly has a procoagulant action, unlike the others factor X analogues.

This result is confirmed by Fig. 4 of the present application which compares the procoagulant effect of the GDC-AVG analogue with the GD-FX analogue in factor VIII-depleted (4A) or factor IX-depleted (4B) plasma.

Fig. 4 shows that in the presence of GDX-AVG analogue, the clotting time is shorter than in presence of GD-FX, which undeniably confirm that GDX-AVG analogue is more active than GD-FX analogue.

The fact that GDX-AVG analogue is more active than the GD-FX indicates that an amplification of thrombin generation has indeed taken place in the presence of GDX-AVG.

The inventors have in fact shown in Example 5 that the GDX-AVG analogue lead to a production of at least 26 times more activated forms of factor X.

In conclusion, Applicants have clearly shown that:

- 1) The GDX-AVG analogue of factor X is efficiently cleaved by thrombin, resulting in the activated form of GDX-AVG analogue;
- 2) the activated form of GDX-AVG analogue provides a high amidolytic activity;
- 3) the activated form of GDX-AVG analogue interacts with factor Va and activate prothrombin;
- 4) the activated form of GDX-AVG analogue has a higher half time than native activated factor X;
- 5) the activated form of GDX-AVG has a procoagulant activity; and
- 6) the activated form of GDX-AVG analogue establishes an autoamplification of thrombin generation.

In view of the foregoing, Applicants submit that they have clearly met the burden of establishing that the present invention of an analogue of factor X which has the unexpected result of bypassing the deficient steps of the clotting cascade. This invention was borne by overcoming the drawbacks of the currently used therapeutic approaches but also establish auto-amplification of thrombin generation in subject suffering from haemophilia. There is no

disclosure or suggestion in Himmelspace et al to select the very specific analogue with a sequence VPR-AVG in the activation peptide, among all factor X analogues disclosed in Himmelspace et al.

Accordingly, Applicants submit that it would not be obvious for the skilled artisan to identify which analogue of factor X might comply with the above mentioned characteristics. As such, Himmelspace et al fails to render the presently claimed invention obvious.

Withdrawal of these grounds of rejection is requested.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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